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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,486	12/12/2006	Annie Andrieux	128765	4235

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EXAMINER	
CORNET, JEAN P	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
10/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,486	ANDRIEUX ET AL.	
	Examiner	Art Unit	
	JEAN CORNET	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 15-38 are pending. Claims 1-14 are cancelled by Applicants. New claims 26-38 are added. Claims 15-38 are currently under examination on the merit.

2. Applicant's arguments filed 08/14/2009 have been fully considered. Rejections and objections not reiterated form previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "for a patient in need thereof" is unclear. What is the population of patient? Who is the patient? The patient is in need of what? Since Schizophrenia is specie of a psychiatric disorder as disclosed in Applicant's specification (page 4, line 1-15) This would be interpreted as a patient in need of such treatment.

. *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-38 are rejected under 35 U.S.C. 112, second paragraph, for lacking enablement for the full scope of the claims. The specification is enabling for a method of treatment of a disease involving behavior disorders in an animal model of psychiatric disease (STOP mice) by administering an effective amount of epothilone D. However, the specification is not enabling for the treatment of other neural connectivity disorder in individuals in general, which could include autism with epothilones.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404).

The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a

fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of treatment of a disease involving a neuronal connectivity defect comprising administering to an individual in need thereof an effective amount of epothilones. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treatment of a disease involving a neuronal connectivity defect comprising administering to an individual in need thereof an effective amount of epothilones.

Guidance in the specification and Working Examples

The specification teaches that effect of epothilone D on spontaneous activity, behavioral analysis, and synaptic vesicle density on STOP KO mice. Moreover the specification provides guidance on how the STOP deficiency mice upon administration of epothilone D demonstrate a remarkable decrease in the total number of shifts between activities (see Fig 2) concerned the number of walking and grooming sequences, whereas the number of sleeping and feeding sequence remained unaffected (page 16, lines 16-24). Moreover, the specification shows how when STOP KO female's mice subjected to epothilone D treatment, nurturing was improved in re-establishing maternal abilities compatible with pup survival as compared to the untreated STOP KO mice (page 17). Lastly, there was a 20% increase of the vesicle density of an hippocampus section observed in STOP treated mice with epothilone D versus the untreated mice. .Thus, the specification teaches treatment of STOP KO mice displaying a set of behavioral alteration and neurotransmission defects that are similar to those observed in Schizophrenia. Such limited studies are not considered to be persuasive scientific evidence that the composition is capable of treating autism or other neural connectivity

defect such as bipolar disorder. The specification generally asserts that the efficacy of epothilone D is believed to be due to the beneficial effect on synaptic plasticity of the hypocampal neurons indicating defects any defect in the synaptic transmission such as the one observed in STOP deficit mice would exhibit dramatic perturbation in maternal behavior, hyper-locomotor activity and fragmentation of spontaneous activity, but does not show how this effect is linked to the treatment of all neuronal connectivity defects. Accordingly the specification does not provide adequate guidance as to the treatment of all neuronal connectivity disorders.

Quantity of experimentation

In light of the above, it is considered that a skilled artisan would have to exercise undue experimentation to practice the instant invention. In particular, as the correlation between treatment of autism with epothilones and other diseases such as bipolar disorder, is not known, the skilled practitioner would have to test the compound and/or compound combination as claimed, in each condition and patient falling within the scope of the claim, to determine treatment efficacy for each condition and patient. For example, for each disease state, epothilone composition would have to be selected, and a dosage regimen including dose amount, dosage form, frequency and route of administration would have to be selected. If efficacy of the drug did not result, the dosage regimen would have to be varied, for example by changing the dosage amount, form or route of administration, until efficacy was achieved. If animal models for a particular condition exist, then these could be utilized for testing, however if no animal

models exist, then toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the treatment of a particular condition was shown, another composition meeting the limitations of the claims would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compositions as claimed for the particular condition, the process would have to be repeated for at least the other conditions disclosed by Applicants, including autism, as well as any other conditions associated with neuronal connectivity defects, such as bipolar disorder. The process would then have to be repeated for all other *mammals* as claimed, such as veterinary patients, which process could also involve developing methods of identifying and diagnosing the same or analogous respiratory conditions in such mammal patients if not already known. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there are any challenges remain to be resolved with autism. The online Merck manuals accessed on 10/26/09 teach that the specific causes of autism known as autism spectrum disorder are not fully understood, although they are clearly biologically determined. Drug therapy can not change the underlying disorder; however, drugs such as serotonin reuptake inhibitors and antipsychotic drugs are often in reducing the

symptoms associated with the behaviors. Buitelaar et al. (European Child and Adolescent psychiatri 9; I/85-97, Steinkopff Verlag (2000)) teach the neurochemical basis of autism is unknown; there is as yet no place for a pharmacotherapy based on defined pathogenesis of the core social and communicative deficits (page I89, left col., last para.). Further Buitelaar et al teach that medications are used to only treat the behavioral symptoms, see table 1. Specifically, Posey et al. (Exp Opin. Pharmacother. (2001) 2(4):587-600) teach that there are no medication that are specifically marketed for the treatment of autism, but there does exist however medications that are often treat symptoms assciated with autism (abstract). Thus, while considerable research has gone into to identify certain compounds as therapeutic targets, one of skill in the art would recognize that a considerable amount of in vivo empirical testing is required, after the selection of a potential therapeutic agent by testing it onto animals.

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vitro environment as compared to the very narrowly defined and controlled conditions of an in- vivo testing does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells,

over a period time, lose phenotypic characteristics associated with their normal counterpart cell type.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for the treatment of other neuronal connectivity defects such as autism, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In conclusion

5. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEAN CORNET whose telephone number is (571)270-7669. The examiner can normally be reached on Monday-Thursday 7.00am-5.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)? If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JC/

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642